

HIGH RESOLUTION MASS SPECTROMETRY
IN FRAGMENTATION STUDIES
OF SESQUITERPENES AND RELATED COMPOUNDS:

THE MECHANISM OF FRAGMENTATION
UNDER ELECTRON IMPACT OF WIDDROL^{1, 2}

By

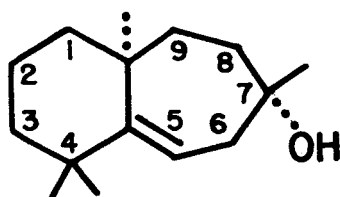
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ABSTRACT

The mass spectrum of the sesquiterpenol widdrol is dominated by the peak at m/e 151, corresponding to the charged species formed by loss of 71 mass units from the molecular ion. A reasonable mechanism for the genesis of the ion of mass 151 is offered by the fragmentation sequence characteristic of alicyclic alcohols. However, the mass spectra of a series of deuterium-labeled analogs of widdrol and the complete high resolution mass spectra of these compounds indicate that most of the $M-71^+$ ions arise from a rearranged "ketonic" molecular ion, rather than from the alicyclic alcoholic molecular ion. This extensive rearrangement of the molecular ion derives from the presence of the homoallylic double bond to which the hydroxyl hydrogen is transferred through a six-membered intermediate.

INTRODUCTION

The structure and absolute configuration of widdrol were established after much discussion in 1961.⁵ In 1964, Dauben and Friedrich⁶ demonstrated the mechanism of conversion of thujopsene to widdrol in aqueous acid. In the course of their investigation they produced 6, 6- d_2 -widdrol and 8, 8- d_2 -widdrol. The availability of these two isotopically-labeled analogs, coupled with the determination of complete high resolution mass spectral data,⁷ has made possible a thorough study of the fragmentation under electron impact of this natural product.



WIDDROL

EXPERIMENTAL

Widdrol-OD was obtained by exchanging a sample of widdrol on a D_2O -treated VPC column⁸ and co-inserting it into the mass spectrometer with a microliter of heavy water. Its isotopic purity was calculated from the spectrum to be 83% d_1 and 17% d_0 . The isotopic purity of 6, 6-widdrol is reported by Dauben⁶ to be 93% d_2 , and that of the 8, 8- d_2 -widdrol used is reported⁶ as 43% d_2 and 43% d_1 .

The low resolution mass spectra of widdrol, widdrol-OD, 6, 6- d_2 -widdrol and 8, 8- d_2 -widdrol were measured on a modified⁹ CEC-21-103C mass spectrometer with the inlet system at 100° and the source at 180° . The high resolution mass spectrum of widdrol was obtained on a CEC-21-110 mass spectrometer operating with the inlet system at 180° and the source at 200° . In the spectrum presented the masses are plotted in methylene units.⁷ On the abscissa each major division marker corresponds to the saturated ion, e.g. C_nH_{2n+1} , with the number of carbon atoms given in the top row of figures and the number of hydrogen atoms indicated in the bottom row. There

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are fourteen units between each major division; to obtain the number of hydrogen atoms in an unsaturated or cyclic ion, start at the position of the saturated ion of appropriate carbon-number and count backwards.

DISCUSSION

If widdrol is viewed as a cyclic alcohol, it would be expected to undergo the characteristic fragmentation sequence outlined for alicyclic alcohols by Natalis¹⁰ and demonstrated by use of deuterium-labeled analogs for cyclopentanol¹¹ and cyclohexanol.¹² Thus the molecular ion should suffer bond scission alpha to the hydroxyl group with transfer of an α -hydrogen from the other side, accompanied by cleavage of the γ -bond. This sequence occurs in the fragmentation of widdrol, (Scheme I) producing the ion of mass 71. The origin of this ion is supported by the high resolution spectrum of widdrol, which indicates that about 80% of the peak at m/e 71 arises from ions with the composition $C_4H_7O^+$ and is confirmed by the spectra of the labeled compounds. In the spectrum of 6, 6-d₂-widdrol the peak at m/e 71 remains at m/e 71, demonstrating that the ion does not contain deuterium atoms from C-6. In the spectrum of 8, 8-d₂-widdrol most of the peak at m/e 71 moves to m/e 72 after correction for the isotopic distribution⁶ and contributions from $C_5H_{11}^+$ ions. Thus one of the two deuterium atoms at C-8 is retained in this fragment. Similarly in the mass spectrum of widdrol-OD about 80% of the peak at m/e 71 moves to m/e 72 (after correction for contributions from $C_5H_{11}^+$ ions and isotopic purity), confirming the retention of the hydroxyl deuterium atom in 80% of the oxygen-containing ions of mass 71. Some of the charge is retained on the hydrocarbon moiety in this cleavage, contributing about 15% of the intensity of the peak at m/e 151 in the spectrum of widdrol-OD.

There is another major cleavage sequence apparent in the mass spectrum of widdrol. This second mode of fragmentation derives from the presence of the homoallylic double bond. The hydroxyl hydrogen is transferred to the double bond through a six-membered intermediate, and the molecular ion opens into the "methyl ketone" ion (Scheme II). The "ketonic" ion then fragments exactly as one would predict. α -Cleavage produces ions of mass 43 and composition $C_2H_3O^+$, which account for about 60% of the prominent peak at m/e 43. The $C_2H_3O^+$ ions formed from the three labeled compounds contain no deuterium atoms. A minor portion of the charge is carried by an ion of mass 179. The hydrocarbon peak at m/e 179 moves to m/e 180 in the spectrum of widdrol-OD, to 181 in the spectrum of 6, 6-d₂-widdrol, and to m/e 181 in the spectrum of 8, 8-d₂-widdrol after correction for isotopic purity.

There is no γ -hydrogen in the "ketonic" ion and thus the classical McLafferty rearrangement is inoperative. The mass spectrum of another ketone, which similarly contains no γ -hydrogen, has been discussed by Arndt and Djerassi.¹³ They report that the base peak in the spectrum of 2, 2, 8, 8-tetramethyl-5-nonanone results from scission of the γ -bond at the tertiary center, with retention of the major portion of the charge on the hydrocarbon moiety. This is precisely the cleavage that generates most of the base peak at m/e 151 in the widdrol spectrum (Scheme II). Eighty-five per cent of the peak at m/e 151 appears to derive from the ion formed by scission of the γ -bond at the tertiary center, as that much of the peak moves to m/e 152 (after correction for isotopic purity) in the spectrum of widdrol-OD. The peak occurs at m/e 153 in the spectrum of 6, 6-d₂-widdrol and the major portion remains at m/e 151 in the spectrum of 8, 8-d₂-widdrol. A lesser amount of the charge is carried by the complementary ion, which contributes about 20% of the $C_4H_7O^+$ ions of mass 71, calculated from the spectrum of widdrol-OD.

Thus fragmentation can be distinguished in the mass spectrum of widdrol from two different molecular ions, which both produce daughter ions of the same mass and composition in their major fragmentation processes. In one case the hydroxyl hydrogen is transferred and the charge remains primarily on the hydrocarbon moiety — in the other case a ring hydrogen is transferred and most of the charge remains on the oxygen-containing fragment.

Rearrangement of the molecular ion of a β , γ -unsaturated alcohol under electron impact is not unique to widdrol. At least three earlier papers report similar observations on 2-phenylethanol¹⁴ and derivatives,¹⁵ on derivatives of 4-buten-1-ol¹⁵ and on several β -hydroxyesters¹⁶ (see Figures).

It seemed desirable to test the rearrangement in a simple cyclic alcohol, a model compound for the functionalized ring of widdrol. 1-Methyl-cyclohept-3-enol was synthesized and the mass spectra of this alcohol and its deuterated analog were obtained. This compound undergoes the characteristic cyclic alcohol fragmentation — cleavage of the α -bond, transfer of an α -hydrogen from the other side of the

hydroxyl group and scission of the γ -bond — that produces an ion of mass 71 (Scheme III). High resolution mass measurements confirm the composition of the ion as $C_4H_7O^+$. The peak at m/e 71 in the spectrum of 1-methylcyclohept-3-enol appears at m/e 72 in the spectrum of 1-methylcyclohept-3-enol-OD, indicating that the ion retains the hydroxyl deuterium. This β , γ -unsaturated cyclic alcohol also rearranges to the ketonic molecular ion (Scheme IV) as demonstrated by the appearance of an intense peak at m/e 43 in the spectra of both this compound and its OD-analog. High resolution mass measurements reveal that 95% of the ions of mass 43 have the composition $C_2H_3O^+$. Unlike the rearranged widdrol ion, this ketonic ion contains γ -hydrogen, and it can and does undergo the classical McLafferty rearrangement, which generates an ion of mass 58. This enol ion does not contain the hydroxyl deuterium when it is formed from the deuterated alcohol. The complimentary hydrocarbon ion of mass 68 is also formed. Most of the peak at m/e 68 moves to m/e 69 in the spectrum of the OD-analog, indicating that the hydroxyl deuterium is now carried in the hydrocarbon moiety. Thus fragmentation from two molecular ions is also demonstrated for 1-methyl-cyclohept-3-enol. This is one case in which the fragmentation of a model compound does approximate that of the natural product.

FOOTNOTES AND REFERENCES

1. Financial support was provided in part by the National Aeronautics and Space Administration Grant NsG 101.
2. For a more extensive report of these studies, see "High Resolution Mass Spectrometry in Molecular Structure Studies Part IV", C. Fenselau, W. J. Richter, and A. L. Burlingame, J. Am. Chem. Soc., in preparation.
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4. Present address: Hofmann LaRoche Pharmaceutical Company, Basel, Switzerland.
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LOW RESOLUTION MASS SPECTRA

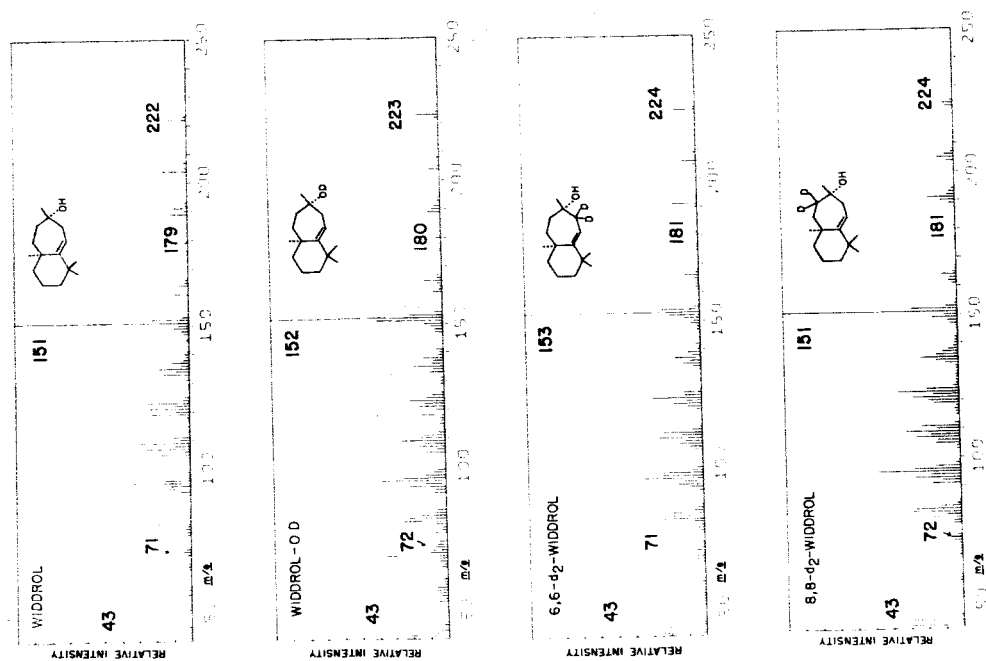


FIGURE 1

HIGH RESOLUTION MASS SPECTRA

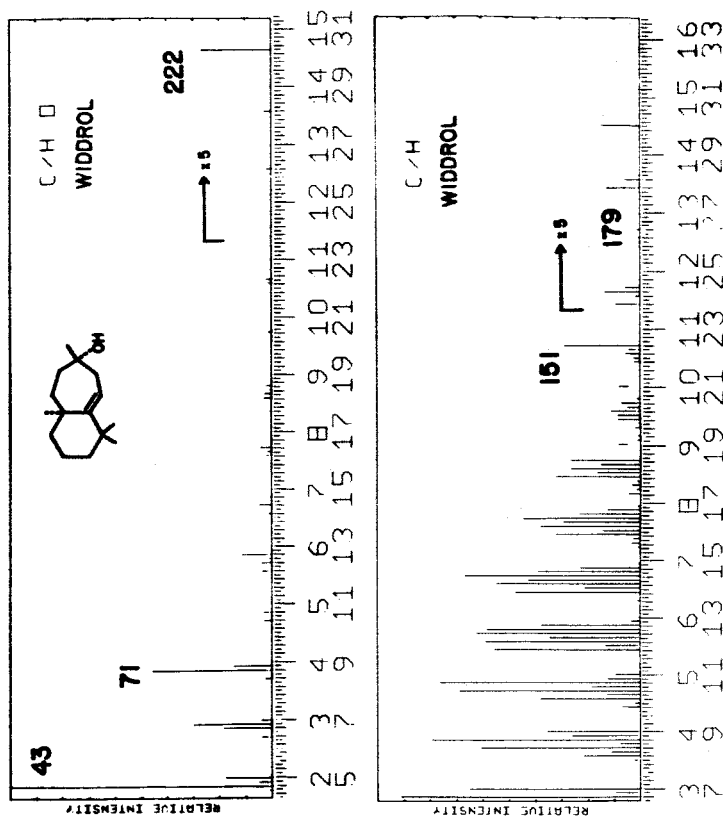
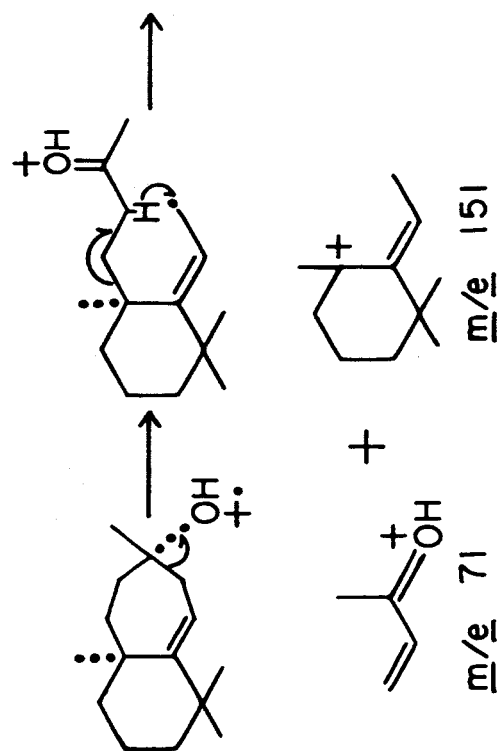
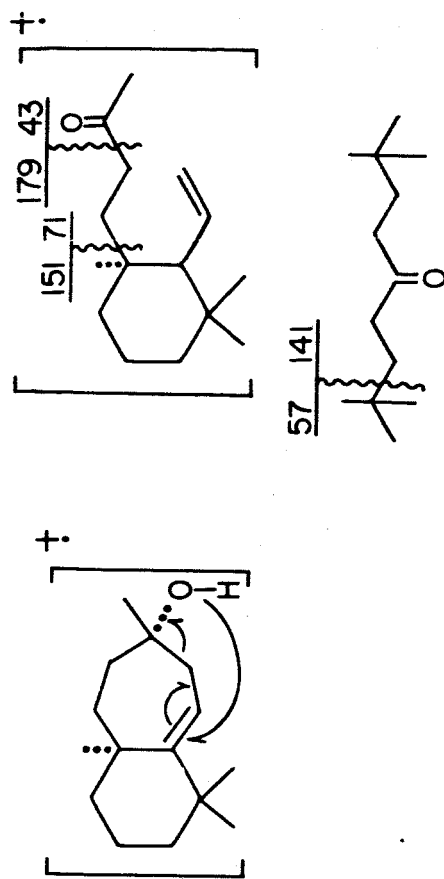


FIGURE 2

SCHEME I

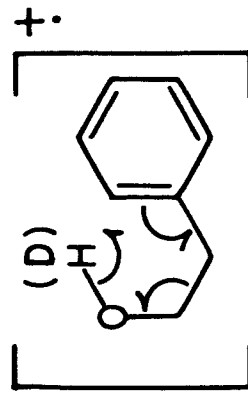


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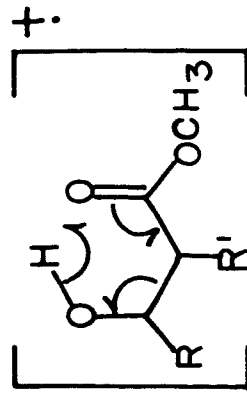


Arndt and Djerassi (1965)

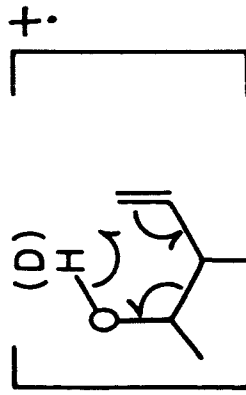
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Gilpin (1958)

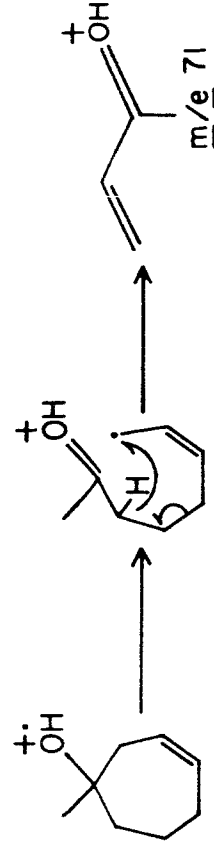


Etémadi (1964)



Audier, et al. (1965)

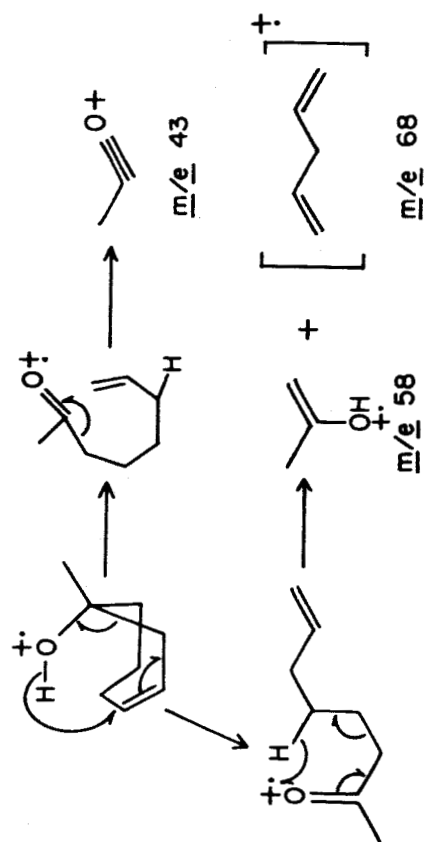
SCHEME III



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SCHEME IV



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